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Registration Decision

RD2015-24

# Flupyradifurone

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## Registration Decision for Flupyradifurone

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting full registration for the sale and use of Flupyradifurone TC and the end-use products BYI 02960 480 FS and Sivanto Prime Insecticide (previously known as Sivanto 200 SL) containing the technical grade active ingredient flupyradifurone to control various insect pests.

An evaluation of available scientific information found that, under the approved conditions of use, the products have value and do not present an unacceptable risk to human health or the environment.

These products were first proposed for registration in the consultation document<sup>1</sup> Proposed Registration Decision PRD2014-20, *Flupyradifurone*. This Registration Decision<sup>2</sup> describes this stage of the PMRA's regulatory process for flupyradifurone and summarizes the Agency's decision, the reasons for it and provides, in Appendix I, a summary of comments received during the consultation process as well as the PMRA's response to these comments. This decision is consistent with the proposed registration decision stated in PRD2014-20.

For more details on the information presented in this Registration Decision, please refer to the PRD2014-20, which contains a detailed evaluation of the information submitted in support of this registration.

## What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable<sup>3</sup> if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions of registration. The Act also requires that products have value<sup>4</sup> when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the

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<sup>1</sup> "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

<sup>2</sup> "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

<sup>3</sup> "Acceptable risks" as defined by subsection 2(2) of *Pest Control Products Act*.

<sup>4</sup> "Value" as defined by subsection 2(1) of *Pest Control Products Act* "... the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact".

nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at [healthcanada.gc.ca/pmra](http://healthcanada.gc.ca/pmra).

## **What is Flupyradifurone?**

Flupyradifurone is an insecticide in a new Mode of Action (MoA) Subgroup (Subgroup 4D, the Butenolides), that interferes with the function of insect nerves. MoA Group 4 also includes the neonicotinoids (4A), nicotine (4B) and sulfoxaflor (4C). Flupyradifurone is active by ingestion and contact, but is more potent via ingestion. This active ingredient is systemic when applied as a soil treatment and has translaminar activity when applied as a foliar treatment. Formulated as BYI 02960 480 FS and used to treat soybean seeds, it controls soybean aphids and adult bean leaf beetles. Formulated as Sivanto Prime Insecticide and sprayed on the foliage of various field, vegetable, fruit and nut crops (for example, leafy vegetables, legumes, fruiting vegetables, cucurbits (except cantaloupe), pome fruit, berries, tree nuts, corn, alfalfa, peanut and hops), flupyradifurone controls aphids, leafhoppers, scale insects, whiteflies, Colorado potato beetle, and blueberry maggot and suppresses pear psylla. When applied as a soil application to fruiting vegetables, cucurbits (except cantaloupe) and berries and small fruits, Sivanto Prime Insecticide controls aphids, leafhopper and whiteflies. This product can be applied by air to tuberous, corm, root and legume vegetables.

## **Health Considerations**

### **Can Approved Uses of Flupyradifurone Affect Human Health?**

**Products containing flupyradifurone are unlikely to affect your health when used according to label directions.**

Potential exposure to flupyradifurone may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, flupyradifurone was slightly acutely toxic via the oral route; therefore the signal word and hazard statement "CAUTION – POISON" are required on the label. Flupyradifurone was demonstrated to be of low acute toxicity via the dermal and inhalation

routes, non-irritating to skin, and minimally irritating to eyes. The potential for flupyradifurone to cause an allergic skin reaction could not be ruled out based on the information provided; therefore, the hazard statement "POTENTIAL SKIN SENSITIZER" is required on the label for the active ingredient.

Sivanto Prime Insecticide, one of the end-use products containing flupyradifurone, was demonstrated to be of low acute toxicity via the oral, dermal and inhalation routes. It was determined to be non-irritating to the skin and minimally irritating to the eye. Sivanto Prime Insecticide did cause an allergic skin reaction; therefore, the hazard statement "POTENTIAL SKIN SENSITIZER" is required on the label for this end-use product.

BYI 02960 480 FS, the other end-use product containing flupyradifurone, was demonstrated to be slightly acutely toxic via the oral route; therefore, the signal word and hazard statement "CAUTION – POISON" are required on the label. BYI 02960 480 FS was determined to be of low acute toxicity via the dermal and inhalation routes, minimally irritating to the skin and non-irritating to the eye, and did not cause an allergic skin reaction.

Registrant-supplied short-, and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature were assessed for the potential of flupyradifurone to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment included generalized signs of toxicity as well as effects on body weight, skeletal muscle, and fetal survival. There was no evidence to suggest that flupyradifurone was genotoxic or causes cancer. The risk assessment protects against the effects noted above and any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in test animals.

#### **Residues in Water and Food**

##### **Dietary risks from food and drinking water are not of health concern.**

Refined aggregate dietary intake estimates (food plus drinking water) revealed that children 1 to 2 years of age, the highest exposed subpopulation, are expected to be exposed to less than 31% of the acceptable daily intake. Based on these estimates, the refined chronic dietary risk from flupyradifurone is not of health concern for all population subgroups.

Refined acute dietary (food plus drinking water) intake estimate was less than 26% of the acute reference dose for children 1 to 2 years of age, the highest exposed subpopulation. The refined aggregate exposure from food and drinking water is considered acceptable for females 13 to 49 years of age at 24% of the acute reference dose.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada, the United States, and Brazil (coffee) using flupyradifurone on a range of representative commodities were deemed acceptable. The MRLs for this active ingredient can be found in the Science Evaluation of the consultation document, PRD2014-20.

### **Risks in Residential and Other Non-Occupational Environments**

Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings. Therefore, bystander exposure is expected to be minimal.

The occupational re-entry worker exposure to treated crops was not of concern and is expected to address any potential exposure to bystanders in a pick-your-own (PYO) scenario.

### **Occupational Risks From Handling Flupyradifurone**

**Occupational risks are not of concern when flupyradifurone is used according to the proposed label directions, which include protective measures.**

Workers in commercial seed treatment facilities (and mobile treaters) and farmers handling seed treated with BYI 02960 480 FS can come into direct contact with flupyradifurone through residues on the skin and through inhaling dust. Therefore, the label states that treaters/applicators must wear long-sleeved shirt, long pants, chemical resistant gloves and shoes plus socks. Baggers and others involved in packaging the treated seed must wear long-sleeved shirt, long pants, gloves and shoes plus socks. Cleanout/repair personnel must wear coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, and shoes plus socks. Soybean seeds can only be treated in closed treatment systems. Farmers planting and handling treated seed must wear long-sleeved shirt, long pants, chemical-resistant gloves, and shoes plus socks. Planters must use a closed cab tractor.

Farmers and custom applicators who mix, load and apply Sivanto Prime Insecticide as a foliar or soil treatment and field workers re-entering treated fields can come in direct contact with flupyradifurone residues on the skin and/or through inhalation. Therefore, the label specifies that anyone mixing/loading and applying flupyradifurone must wear long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks. The label also requires that workers not enter treated fields for 12 hours after application except for hand girdling of table grapes where workers cannot re-enter for 24 hours.

Taking into consideration these label statements, precautionary measures, and the exposure duration for handlers and workers, it was determined that the risks to these individuals are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

## **Environmental Considerations**

### **What Happens When Flupyradifurone is Introduced Into the Environment?**

**When used according to label direction flupyradifurone is not expected to pose an unacceptable risk to the environment.**

Flupyradifurone can enter the environment when it is used as an insecticide for control of a large number of pests in a variety of crops. It can be applied as a foliar spray, as a soil drench and as a seed treatment. Flupyradifurone is a systemic insecticide and is taken up and transported throughout plant tissues.

In the terrestrial environment, flupyradifurone is broken down primarily by soil microorganisms. Field and laboratory studies indicate that flupyradifurone can persist in soil and has a potential to carryover to the following growing season. In soil flupyradifurone breaks down into two major transformation products, 6-chloronicotinic acid (6-CNA) and difluroacetic acid (DFA). 6-CNA breaks down rapidly while DFA can persist in soil. Flupyradifurone is not volatile and unlikely to enter the atmosphere. Flupyradifurone and the transformation product DFA have the potential to move through soil to enter groundwater, but groundwater modelling based on chemical fate data and conservative assumptions indicate that flupyradifurone will not enter groundwater at levels that could pose unacceptable risk to human health or the environment. Flupyradifurone and its breakdown products can enter aquatic environment through surface run-off and spray drift. In the aquatic environment, flupyradifurone mixes readily with water and can be persistent. It is broken down primarily by reaction with sunlight, producing BYI 02960-succinamide and azabicyclosuccinamide. Flupyradifurone residues are not expected to accumulate in fish tissues.

Flupyradifurone and its major transformation products pose a negligible risk to soil dwelling organisms, terrestrial and aquatic plants, birds and small wild mammals, freshwater algae, fish (freshwater and marine), and amphibians when applied by foliar and soil drench applications. Flupyradifurone could pose a risk to some species of non-target arthropods and aquatic invertebrates if they come in contact with high enough residue levels. Flupyradifurone may also pose a risk to certain small mammals if they consume enough treated seeds. While flupyradifurone is unlikely to pose a risk to bee colonies, it may have transitory effects on adult foraging bees when applied during full bloom by foliar application. In order to mitigate any risks to bees and other non-target organisms, risk reduction measures will be outlined on the label. With these measures in place the risks to the environment are not of concern.

## **Value Considerations**

### **What Is the Value of Flupyradifurone?**

#### **BYI 02960 480 FS**

**Applied to soybean seeds, BYI 02960 480 FS provides early season protection of seedlings against soybean aphids and adult bean leaf beetles, which are major pests of soybean and may be vectors of soybean viruses.**

The value of BYI 02960 480 FS is based on several considerations. It provides early season protection of soybean seedlings against soybean aphid and adult bean leaf beetles, which may cause an economic impact when these pests are present at economic thresholds. Soybean aphids and bean leaf beetles are important pests of soybean and may be vectors of soybean viruses. BYI 02960 480 FS also has value because it provides a new MoA Subgroup (Subgroup 4D, the Butenolides) for control of these pests. Other active ingredients in the broader MOA Group 4 are registered for use on soybean against these pests. However, this new mode of action subgroup may help users with resistance management, making it a useful addition to a pest management system.

#### **Sivanto Prime Insecticide**

**Sprayed on a variety of outdoor crops, Sivanto Prime Insecticide controls aphids, leafhoppers, scale insects, whiteflies, Colorado potato beetle, and blueberry maggot and suppresses pear psylla. Applied as a soil treatment to fruiting vegetables, cucurbits, and berries and small fruit, Sivanto Prime Insecticide controls aphids, leafhoppers and whiteflies. Many of these are important agricultural pests. Flupyradifurone has been identified as a potential replacement product for active ingredients being phased out as a result of re-evaluation.**

Sivanto Prime Insecticide has value based on several factors. As a foliar application, Sivanto Prime Insecticide controls several serious pests on many outdoor crops. Pests which Sivanto Prime Insecticide can be used against include whiteflies, an emerging pest of outdoor crops in Canada; aphids and leafhoppers, which are major pests of a variety of outdoor crops; scale insects, important pests of pome fruits which are considered difficult to control; blueberry maggot, an important pest of blueberries; Colorado potato beetle, an important pest of potato and fruiting vegetables; and pear psylla, an important pest of pear. Soil applications of Sivanto Prime Insecticide to fruiting vegetables, cucurbits, and berries and small fruit control aphids, leafhoppers and whiteflies.

Many of the labelled pests have developed resistance to some long-established pest control products, and Sivanto Prime Insecticide provides a new mode of action subgroup for use against these pests. Although other active ingredients in the broader MOA Group 4 are registered for use on many of these crops and pests, this new mode of action subgroup may help users with resistance management, which is an important consideration for sustainable pest control. An

additional value consideration is that flupyradifurone has been identified as a potential replacement product for diazinon and endosulfan, active ingredients which are being phased out for many pest/crop combinations due to health or environmental concerns, thus providing growers with access to a new product to control many of the same pests.

## **Measures to Minimize Risk**

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures on the label of BYI 02960 480 FS and Sivanto Prime Insecticide to address the potential risks identified in this assessment are as follows:

### **Key Risk-Reduction Measures**

#### **Human Health**

As direct contact with flupyradifurone on the skin or through inhalation of spray mists can occur, anyone mixing, loading and applying BYI 02960 480 FS in commercial seed treatment facilities (and mobile treaters) must use closed treatment systems only. To reduce exposure, treaters/applicators must wear long-sleeved shirt, long pants, chemical resistant gloves and shoes plus socks. Baggers and others involved in packaging the treated seed must wear long-sleeved shirt, long pants, gloves and shoes plus socks. Cleanout/repair personnel must wear coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, and shoes plus socks. Workers planting and handling treated soybean seed on the farm must wear long-sleeved shirt, long pants, chemical-resistant gloves, and shoes plus socks and plant using a closed cab tractor.

Workers mixing, loading and applying Sivanto Prime Insecticide as a foliar or soil application through ground application equipment or chemigation systems must wear long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks.

#### **Environment**

Flupyradifurone product labels inform the user of the leaching, surface run-off and carry-over potentials of flupyradifurone and of the measures to mitigate potential exposure to terrestrial and aquatic insects including bees. Specific mitigation measures are:

- To mitigate the potential exposure of beneficial arthropods, measures to reduce drift are required on the label of Sivanto Prime Insecticide.
- To mitigate potential exposure of aquatic organisms through spray drift, spray buffer zones of 1-10 metres to protect sensitive aquatic habitats are specified on the label of Sivanto Prime Insecticide. Instructions for reducing run-off are required on the label of Sivanto Prime Insecticide.

- To mitigate the potential transitory effects of flupyradifurone to bees, foliar applications are to be made in the early morning or evening when bees are not actively foraging, and measures to reduce drift are to be followed, as specified on the label of Sivanto Prime Insecticide.
- To minimize potential exposure of small wild mammals through ingestion of treated seeds, hazard statements are required on the label and on the tags of bags containing treated seeds. Guidance to reduce the availability (quillc) of treated seeds and Best Management Practices are required on the label of DVI 02960 480 FS.
- To minimize the potential of flupyradifurone and its transformation product difluoromethoxy acid (DFA) to enter ground water, a statement is required on the Sivanto Prime Insecticide label informing users of the leaching potential of this chemical and identifying soil and water table conditions that may result in ground water contamination (permeable soils, shallow water table).
- To minimize the potential of flupyradifurone to be carried over to the following growing season, a statement is required on Sivanto Prime Insecticide label informing users of the carry-over potential of this chemical and recommending that flupyradifurone not be used in areas treated with the product during the previous season.

When taking these use restrictions and precautionary measures into consideration, the risk to the environment including beneficial insects and bees is not of concern.

### Other Information

The relevant test data on which the decision is based (as referenced in PRD2014-20) are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail ([pmra.inform@hc-sc.gc.ca](mailto:pmra.inform@hc-sc.gc.ca)).

Any person may file a notice of objection<sup>5</sup> regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of the Health Canada's website (*Request a Reconsideration of Decision*) or contact the PMRA's Pest Management Information Service.

<sup>5</sup> See section 15(1) of the *Pest Control Products Act*.

## Appendix 1

### Comments and Responses

In response to the consultation document PMDS006-20, *Flupyradifurone*, comments were received from stakeholders, including non-government organizations and the public. A number of comments expressed similar concerns and were, therefore, consolidated and summarized, with responses provided below.

#### **I. Comments relating to approval of flupyradifurone and potential health effects.**

Several comments were received in which concern was expressed over the approval of flupyradifurone for use in Canada and the potential for adverse health effects in humans, including children. In particular, questions were raised about the potential for neurotoxic effects (one comment raised concerns about potential neurological conditions such as Alzheimer's and autism) and bioaccumulation following exposure to flupyradifurone, and comments were made pertaining to the level of knowledge regarding short-term and long-term health effects of flupyradifurone. One commenter highlighted the lack of a repeated-dosing regimen in the toxicokinetics studies in rats, implying that this demonstrates inadequacies in the testing for the long-term health impacts of flupyradifurone.

#### **PMRA Response**

As outlined in PMDS006-20, a complete and comprehensive toxicology database is available for flupyradifurone. The toxicology studies that have been conducted with flupyradifurone assessed a variety of endpoints and mammalian systems, allowing for a thorough characterization of the potential hazards associated with this active ingredient. The database included short- and long-term dosing studies and studies designed specifically to assess neurotoxicity. Effects observed after long-term dosing included effects on the liver, thyroid gland, kidney and skeletal muscle.

Flupyradifurone produced clinical signs indicative of neurotoxicity following administration by gavage of a single dose; however, none of these clinical signs were found in the dietary feeding studies, including the 90-day neurotoxicity study. Some effects on behavioural observations were reported in offspring in the rat developmental neurotoxicity (DNT) study. The concern for these findings was low, however, given that the magnitude of the effects was marginal, the findings were observed in only one sex and at only one time point, and they occurred at a high dose level relative to the dose levels used as points of departure (PODs) for the health risk assessment. Although the neurotoxicity studies are not designed to assess a chemical's potential to produce neurological conditions such as Alzheimer's and autism, the overall evidence in the flupyradifurone toxicology database does not support an association between these neurological conditions and exposure to flupyradifurone. The health risk assessment ensures that the level of potential human exposure to flupyradifurone remains well below the dose levels that resulted in any adverse effects in the toxicology studies.

Extensive testing of the toxicokinetics following single dose was conducted. The lack of a repeated dosing regimen in the assessment of toxicokinetics was not considered to be a deficiency. Toxicokinetic studies provide information that is useful in the hazard assessment of pesticides, but long-term toxicity studies conducted with flupyradifurone are available, which provide information relating to the potential long-term health effects of exposure to flupyradifurone.

### 3. Comments relating to the target margin of exposure.

A comment was made that the "target margin of effect (MOE)" of 100 used in the human health risk assessment is a low value and is not consistent with requirements under the *Pest Control Products Act* (2002) for an additional extrapolation factor to protect vulnerable populations. The commenters argued that a "MOE" of 100 does not encompass inter-individual variability, and it ignores the intention of the new Act.

### PMRA's Response

It should be clarified that the PMRA used a target margin of exposure (MOE) of 100 in the occupational risk assessment for flupyradifurone, a Composite Assessment Factor (CAF) of 100 in the chronic dietary assessment, and a CAF of 300 in the acute dietary assessment. These values were deemed to be appropriate based on an assessment of all available data, and include factors to address the uncertainty inherent in the extrapolation of information from experimental animal species to humans as well as the potential variability in response within the human population. This approach is consistent with the practices of most regulatory authorities.

As outlined in PM2010-020, the requirements under the *Pest Control Products Act* were considered and applied to the establishment of toxicological endpoints and assessment factors in the dietary assessments for flupyradifurone. A *Pest Control Products Act* factor of 5-fold was applied to the toxicological endpoint selected for the acute dietary exposure assessment in order to afford protection against the developmental effects observed in the dose range-finding and main effect developmental toxicity studies.

While the *Pest Control Products Act* does not specifically require the application of an additional factor in occupational risk assessment, there is potential for indirect exposure to offspring of pregnant or lactating workers. Therefore, in keeping with the spirit of the legislation, it is necessary to protect these indirectly exposed young to a similar degree as their counterparts that are afforded protection through the application of the *Pest Control Products Act* factor. This approach was applied to the human health risk assessment for flupyradifurone. Specifically, the toxicological endpoint and assessment factors (for example, uncertainty factors and the *Pest Control Products Act* factor) selected for chronic dietary and occupational exposure assessment are considered to be protective as they provide a margin of 300 to the MOE for developmental effects observed in the infant.

### 3. Comment relating to the use of NOAELs as opposed to NOELs in the human health risk assessment.

A comment was made expressing concern over the use of no-observed-adverse-effect levels (NOAELs) rather than no-observed-effect-levels (NOELs) as points of departure in the human health risk assessment. The reason provided for this concern was that non-adverse effects would be concerning, for instance for parents (for example, lower activity levels or watery eyes), and that the use of NOAELs inflates the allowable levels of pesticide exposures.

#### PMRA Response

An adverse effect is commonly defined as "a change in morphology, physiology, growth, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influence."<sup>6</sup> Adverse effects include behavioural changes such as changes in activity levels. Conversely, NOELs are typically based on normal biological responses (for example, sweating in exercise) and often represent normal homeostatic reactions to stimuli.

The process of hazard identification, characterization and use of the NOAEL as a point-of-departure (POD) for the purpose of risk assessment by the PMRA is consistent with internationally accepted practices for conducting health risk assessments.<sup>7</sup> The hazard identification and characterization phase involves understanding the inherent properties of a chemical that may lead to adverse responses prior to determining the POD.

### 4. Comment relating to the duration of toxicology studies.

One commenter questioned the validity of the period of exposure in the various toxicology studies (for example, 28 days, 90 days and one year). The commenter noted that the length of exposure may have been too short in studies in which no major effects were observed.

#### PMRA Response

The PMRA requires that an extensive battery of toxicity studies be conducted to determine the nature and extent of the hazard posed by a pesticide. The required studies are designed to assess the possible adverse health effects on a variety of species that may result from single, multiple or lifetime exposure to a pesticide.

<sup>6</sup> International Programme on Chemical Safety. 1994. Environmental Health Criteria 170. Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-Based Exposure Limits. Geneva, Switzerland, World Health Organization, International Programme on Chemical Safety. [www.inchem.org/documents/ehc/ehc/ehc170.htm](http://www.inchem.org/documents/ehc/ehc/ehc170.htm)

<sup>7</sup> International Programme on Chemical Safety. 1999. Environmental Health Criteria 210. Principles for the Assessment of Risks to Human Health from Exposure to Chemicals. Geneva, Switzerland, World Health Organization, International Programme on Chemical Safety. [www.inchem.org/documents/ehc/ehc/ehc210.htm](http://www.inchem.org/documents/ehc/ehc/ehc210.htm)

Short-term toxicity studies determine the effects of repeated exposure to a pesticide over a short period of time, usually from three weeks to three months. A short-term study has been defined as having a duration lasting up to 10% of the animal's lifespan (for example, 90 days in rats, 1 year in dogs).

Long-term daily repeated exposure studies are generally designed to investigate the chronic toxicity and oncogenic potential of the pest control product when administered to test animals over the major portion of their lifespan (for example, 2 years for rats, 18 months to 2 years for mice).

The toxicology database for flupyradifurone included several short-term and long-term toxicity studies, all of which utilized dose levels that were sufficient to produce adverse health effects.

#### **5. Comment relating to the lack of a repeated-exposure inhalation study.**

A comment was made that the fact that the requirement for a repeated-exposure inhalation study on rats was waived owing to low volatility. The commenter claimed that this contradicts the statement in PRD2014-20 that a repeated-exposure inhalation study may be required for future use expansions of flupyradifurone.

#### **PMRA Response**

It should be noted, as stated in PRD2014-20 that a waiver for the requirement for a repeated-exposure inhalation study with flupyradifurone was accepted specifically for the currently petitioned uses, and was not based solely on the low volatility, but was also based on the margins of exposure calculated when using a toxicological endpoint from an oral toxicity study. The requirement for a repeated-exposure inhalation study will be revisited in the event that use expansions are proposed in the future, with consideration of the potential for inhalation exposure related to those uses.

#### **6. Comment relating to thyroid gland effects in the dog.**

A comment was received regarding the statement made in PRD2014-20 that the thyroid gland was a target organ of toxicity in dogs. It was indicated that the thyroid gland effects were only observed in dogs in the 28-day toxicity study, and were limited to enlarged thyroid gland in 2/2 female dogs and increased thyroid weight and follicular dilatation in 1/2 females. No effects on the thyroid gland were observed in the 90-day or one-year toxicity study in dogs. The comment was made that high dose thyroid effects observed at low incidences only in females do not warrant reference of the thyroid gland being a target organ of toxicity in the dog.

#### **PMRA Response**

The PMRA acknowledges that the effects on the thyroid gland observed in dogs were limited to female dogs at the highest dose tested in the 28-day dietary study. No effects on the thyroid gland were observed in dogs in the 90-day or one-year dietary studies; however, the highest doses tested in these two studies were slightly lower than the highest dose tested in the 28-day dietary study.

In the 28-day dietary study in dogs, thyroid gland weight data were only available for a single female as the thyroid gland for the second female at this dose was listed as being missing. Upon gross necropsy, the thyroid gland was enlarged in both female dogs at the highest dose tested. Upon microscopic examination of the thyroid gland, follicular dilatation was observed in one of two females at the highest dose tested.

The text in PRD2014-20 does stipulate that the thyroid effects observed in the dog were noted only at high doses following 28 days of administration. Given the collective weight of the information (for example, the fact that the doses used in the 90-day and one-year dog studies were not as high as those in the 28-day dog study; effects on thyroid gland weight as well as gross and microscopic thyroid gland pathology were observed), the thyroid gland is considered a target of toxicity in the dog despite the findings being limited to one sex at high doses in the 28-day study.

#### **7. Comment relating to the offspring body weight effects in the two-generation reproductive toxicity study.**

A comment was received disputing the NOAEL established by the PMRA for offspring toxicity in the two-generation reproductive toxicity study in rats. The NOAEL for offspring established by the PMRA was the low-dose level of 7.8 mg/kg bw/day, based on decreases in body weight and body weight gain noted in F2 offspring between post-natal day (PND) 14 and PND 21 at the mid-dose level of 39 mg/kg bw/day.

The commenter argued that statistically significant decreases in body weight were observed in F1 generation parental females at the mid-dose of 39 mg/kg bw/day, the same dose level that resulted in reduced F2 pup body weights. The commenter notes that, since the body weight decreases observed in the F1 females were comparable in magnitude to those seen in F2 pups at the same dose level, the conclusion that the study shows evidence of sensitivity in the young rat is unwarranted. The commenter concluded that the parental NOAEL should match that for the offspring and that the two-generation reproductive toxicity study shows no evidence of a difference in sensitivity between adults and young.

#### **PMRA Response**

In F1 parental females at the mid-dose level, body weights at the start of the pre-mating period were decreased by 5% compared with controls, and remained decreased at a similar magnitude throughout the 10-week pre-mating period. However, it was concluded that the body weight effects noted in these females reflected their delayed growth during the pre-weaning period and were not a direct effect of treatment during the pre-mating phase. This was based on the fact that the magnitude of the body weight decrease from controls remained constant over the pre-mating period, and relative bodyweight gains (when calculated as a proportion of the animal's initial body weight) were comparable to controls. Based on this analysis, it was concluded that there were no adverse treatment-related effects on F1 parental females at the mid-dose level that resulted from exposure during the pre-mating period. Overall, there were no adverse treatment-related effects on P or F1 parental animals at any time during the study at the mid-dose level.

Therefore, the parental NOAEL was established by the PMRA at the mid-dose level of 39 mg/kg bw/day, and the offspring NOAEL was established by the PMRA at the low-dose level of 7.8 mg/kg bw/day, based on decreases in body weight and body weight gain noted in F2 offspring between post-natal day (PND) 14 and PND 21 at the mid-dose level of 39 mg/kg bw/day, resulting in evidence of sensitivity of the young.

**8. Comment relating to the sperm parameters in the two generation reproductive toxicity study.**

A comment was received pertaining to the text on page 18 of PRD2014-20, which stated that effects on male rats at the highest dose tested in the two-generation reproductive toxicity study included decreased epididymal and testicular sperm counts in the P and/or F1 generation males. The commenter stated that the text implied that the observed decreases in sperm counts are significant, and noted that, although there are trends towards decreased epididymal sperm counts in P and F1 generation males, none of the decreases are statistically significant. The commenter further notes that testicular sperm counts in the high dose F1 males were comparable to counts in control males. The commenter requested that the changes in testicular (P generation only) and epididymal sperm counts at the highest dose tested be described as slight and not statistically significant.

**PMRA Response**

Based on a review of the two-generation reproductive toxicity study in rats, the PMRA concluded that a slight reduction in epididymal sperm count in P and F1 males and in testicular sperm count in F1 males was observed at 1800 ppm. The PMRA agrees that these decreases were slight (11-13% lower than controls) and not statistically significant. In the table entry for the two generation reproductive toxicity study on page 69 of PRD2014-20 the location and generation in which the sperm counts were decreased are further specified.

**9. Comment relating to the text on developmental toxicity in rabbits.**

A comment was received pertaining to the findings in the developmental toxicity studies conducted in rabbits, and their impact on the application of the *Pest Control Products Act* factor in the human health risk assessment. The commenter noted that, in addition to maternal body weight effects, clinical signs in the form of few or no feces were noted in more than half of the maternal animals at 80 mg/kg bw/day in the developmental toxicity dose range-finding study in rabbits. In addition, maternal food consumption was decreased during most of gestation and was statistically decreased gestation days (GD) 6-8 and 8-10.

The commenter further noted that the incidence of fetal deaths at 80 mg/kg bw/day in the developmental toxicity dose range-finding study in rabbits (7.8%) was just beyond the range of historical control data (0.74 to 6.58%). The commenter noted that the historical control range is compiled from definitive, guideline developmental toxicity studies and not dose range-finding studies, which carry greater inherent variability in response due to fewer animals being used compared to definitive studies. The commenter postulated that it is likely that the incidence of fetal deaths observed at 80 mg/kg bw/day in the dose range-finding study would fall within the historical control range for dose range-finding studies.

The commenter concluded that the 3-fold *Pest Control Products Act* factor is unwarranted based on 1) the presence of maternal toxicity, and therefore, a lack of increased susceptibility to the young rabbit, 2) an incidence of fetal death in the dose-range-finding study only slightly higher than the historical control range for guideline studies, and 3) a clear NOAEL of 40 mg/kg bw/day established for fetal toxicity.

### PMRA Response

As indicated in PRD2014-20, the results from both the range-finding and the guideline rabbit developmental toxicity studies were considered together to assess the potential for developmental toxicity in rabbits. In the guideline study with flupyradifurone, no adverse maternal or developmental effects were observed up to the highest dose tested.

For a guideline developmental toxicity study to be considered acceptable for regulatory purposes, the highest dose level should be chosen with the aim of inducing some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering. As only small, non-adverse and transient reductions in maternal body weight gain were observed in the flupyradifurone study, indicating that a higher dose should have been used, the results of the dose range-finding were utilized to supplement those of the main guideline study to ensure that the requirement for a developmental toxicity study in rabbits was satisfied.

The commenter appears to agree with the PMRA's interpretation of treatment-related findings in these studies as well as the PMRA's conclusions with respect to the establishment of maternal and developmental NOAELs and LOAELs in the rabbit. The NOAEL for maternal toxicity in rabbits was established by the PMRA at 40 mg/kg bw/day based on no or few feces, body weight loss GD 6-8, reduced body weight gain, and decreased food consumption GD 6-10 observed at 80 mg/kg bw/day. The NOAEL for developmental toxicity in rabbits was established by the PMRA at 40 mg/kg bw/day based on increased fetal deaths and decreased fetal body weights observed at 80 mg/kg bw/day.

In interpreting the effect on fetal viability in the dose range-finding study, the results in the treated groups with respect to those in the concurrent control group were taken into consideration, along with the historical control data that were provided. The fact that the proportion of fetal deaths in the high dose group (7.8 %) was outside of the range of historical control data provided to the PMRA (0.74 to 6.58%) was taken into consideration in the interpretation of these findings. No historical control data from dose range-finding studies were provided for comparison. More critical to the interpretation of effects in this study is a comparison to the concurrent control group. In the dose range-finding study, the proportion of deaths at the high dose (7.8%) was four times that in the concurrent control group (1.9%). Regardless of where the high dose value falls in relation to the historical control range, there is a concern for the serious developmental effect at the high dose. The concern regarding prenatal toxicity remains even though a clear NOAEL for the effect has been defined.

Taking all of the above into consideration, there is still evidence of an effect in the developing rabbit that was more serious than those seen in the maternal animal. As outlined in PMRA's Science Policy Note SPN2008-01, *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*, the degree of concern for prenatal and postnatal toxicity is increased if the critical endpoint is based on a serious

toxicological effect. Examples of serious endpoints of concern include reduced viability of the young animal. In the case of flupyradifurone, the 3-fold *Pest Control Products Act* factor was retained due to the seriousness of the developmental effect (fetal death) at the same dose level (80 mg/kg bw/day) that resulted in maternal toxicity.

#### **10. Comment relating to the acute oral toxicity in rats of flupyradifurone.**

The comment was made that, according to Organisation for Economic Co-operation and Development (OECD) Test Guideline 423, the results from the acute oral toxicity study in rats conducted with flupyradifurone meet the criteria for the LD<sub>50</sub> cut-off of 2000 mg/kg bw.

#### **PMRA Response**

The acute oral toxicity study in rats with flupyradifurone was conducted using OECD Test Guideline 423, the acute toxic class method. Three rats were used per dosing step. At the first dosing step of 2000 mg/kg bw, one out of three animals died. The successive dosing of another three animals at the same dose of 2000 mg/kg bw dose produced 100% mortality. There was no mortality at 300 mg/kg bw during the study after successive treatment of two groups of three animals each.

Based on the results of this study, flupyradifurone would be considered to have an acute oral LD<sub>50</sub> range of 300 to 2000 mg/kg bw/day for the purposes of classification under the *Globally Harmonized System of Classification and Labeling of Chemicals*. The PMRA acknowledges that OECD Test Guideline 423 allows for further delineation of the LD<sub>50</sub> cut-off value based on the number of mortalities at particular steps along the dosing sequence. However, using scientific judgment, the fact that 4/6 animals (67%) dosed at 2000 mg/kg bw died led the PMRA to conclude that the oral LD<sub>50</sub> value for flupyradifurone would be less than 2000 mg/kg bw, not greater than 2000 mg/kg bw.

On page 66 of PRD2014-20, the acute oral LD<sub>50</sub> for flupyradifurone can be expressed as "300 mg/kg bw < LD<sub>50</sub> < 2000 mg/kg bw". It should be similarly expressed on page 41 of PRD2014-20, under Section 4.2.1, Risks to Terrestrial Organisms. Based on PMRA's acute toxicity classification system, flupyradifurone is classified as being of slight acute toxicity via the oral route.

#### **11. Comment relating to the acute oral toxicity in rats of the metabolite difluoroacetic acid.**

The comment was made that the acute oral LD<sub>50</sub> value for difluoroacetic acid was not presented accurately in PRD2014-20. It is written on page 72 of the PRD2014-20 as "LD<sub>50</sub> = 300-2000 mg/kg bw". Based on the results of the acute oral toxicity study in rats conducted with difluoroacetic acid (2/3 animals died at 2000 mg/kg bw and 0/6 animals died at 300 mg/kg bw), the commenter noted that the LD<sub>50</sub> should be expressed as being greater than 300 mg/kg bw and less than 2000 mg/kg bw (in other words, 300 mg/kg bw < LD<sub>50</sub> < 2000 mg/kg bw).

## PMRA Response

The metabolite difluoroacetic acid was tested for acute oral toxicity in rats using the acute toxic class method. Three rats were used per dosing step. The dosing sequence was started at a dose of 300 mg/kg bw which did not result in any animal deaths. At the next step, a dose of 2000 mg/kg bw was used which resulted in 2/3 animals dying. Finally, another dose of 300 mg/kg bw was used which again did not result in any animal deaths. This dose progression varied from that recommended in the test guideline, in that a second test series at 300 mg/kg bw should have been conducted prior to dosing at 2000 mg/kg bw. Based on the results of this study, the PMRA concluded that the acute oral LD<sub>50</sub> of difluoroacetic acid is greater than 300 mg/kg bw but less than 2000 mg/kg bw.

Therefore, the PMRA agrees with the commenter. On page 72 of PRD2014-20, the acute oral LD<sub>50</sub> values of the metabolite difluoroacetic acid can be expressed as "300 mg/kg bw < LD<sub>50</sub> < 2000 mg/kg bw".

### 12. Comment regarding the choice of the point of departure for occupational risk assessment.

A commenter argued that the NOAEL of 12 mg/kg bw/day from the 90-day dog dietary study is more appropriate as a point of departure for occupational risk assessment than what was selected by the PMRA. The reasons provided by the commenter in support of this statement included the assertion that the 90-day dog study is of a more appropriate duration to assess short- and intermediate-term occupational risk than the one-year dog study, and that the dog studies provide essentially the same critical effect, skeletal myofiber degeneration, on which their respective NOAELs are based. Considering both the 90-day study (NOAEL = 12 mg/kg bw/day; LOAEL = 33/41 mg/kg bw/day in males/females) and one-year study (NOAEL = 7.8 mg/kg bw/day; LOAEL = 28 mg/kg bw/day), the commenter argued that the true NOAEL for skeletal muscle myofiber degeneration in dogs is  $\geq 12$  mg/kg bw/day, but  $< 28$  mg/kg bw/day, the lower of the two LOAELs. Therefore, the NOAEL of 12 mg/kg bw/day is closer to the true NOAEL for the critical effect. The commenter further noted that since the LOAEL for decreased F2 pup body weight (39 mg/kg bw/day) in the two generation reproduction study is higher than the LOAEL of 28 mg/kg bw/day in the one-year dietary study in dogs, the NOAEL of 12 mg/kg bw/day would be protective of body weight changes in F2 pups.

## PMRA Response

The results from both the 90-day and one-year dietary study in dogs, as well as the reproductive toxicity study in rats, were all taken into consideration by the PMRA in the selection of toxicological endpoints for use in occupational risk assessment. Although the LOAEL of 39 mg/kg bw/day for offspring toxicity in the two generation reproductive toxicity study was higher than the lowest LOAEL (28 mg/kg bw/day) determined in the two dog studies, it was felt that the higher NOAEL of 12 mg/kg bw/day established in dogs (from the 90-day dietary study) may not be protective of the offspring effects observed in the two generation reproductive toxicity study, for which the NOAEL of 7.8 mg/kg bw/day was established. Although a dose higher than 7.8 mg/kg bw/day, such as 12 mg/kg bw/day, may not have resulted in adverse effects in the one-year dog or reproductive toxicity studies, there is no certainty that this would be the case. Therefore, similar to the approach taken for the endpoint selected for the chronic dietary risk

assessment, the one-year dietary study in dogs and the two generation reproductive toxicity study in rats were considered as co-critical studies for assessing risk from occupational exposure. This ensured adequate protection against the effects observed in the sensitive sub-population of the developing young. The selection of this endpoint also ensured an adequate margin to the NOAEL for fetal deaths observed in the rabbit developmental toxicity studies.

**13. The following comment was received regarding the rat dermal absorption study.**

The rat in vivo dermal absorption study on flupyradifurone was conducted in accordance with OECD Guideline 427 (Skin absorption: in vivo method), not United States Environmental Protection Agency (USEPA) guideline OPPTS 870.7600. This study was conducted to address risk to occupational exposure in Europe and North America, and the commenter mentioned that he was under the impression that the PMRA accepts OECD guideline compliant studies. The doses used in this study were the neat formulation of 200 g/L (equal to 2 mg/cm<sup>2</sup>) and two dilutions, 0.625 g/L (0.00625 mg/cm<sup>2</sup>) and 0.1 g/L (0.001 mg/cm<sup>2</sup>). According to OECD guidelines, the "amount should normally mimic potential human exposure, typically 1-5 mg/cm<sup>2</sup> for a solid or up to 10 µl/cm<sup>2</sup> for liquids." In the study for flupyradifurone, the neat formulation falls within this recommended range, and the two dilutions tested were intended to estimate potential human exposure from two spray dilutions.

**PMRA Response:**

The statement "however, it was not quantitatively used as the range of doses tested did not comply with USEPA guideline OPPTS 870 7600" will be removed. The study was used to quantitatively establish a dermal absorption value for mixer/loader/applicators. Exceeding the USEPA guidelines for dose selection was not considered a major deficiency and the PMRA does accept OECD guideline studies.

**14. The following comment was received regarding the potentially absorbable residues for dermal absorption.**

Although the commenter understands the rationale for selecting the 168-hour monitoring period for the low dose group, it is not clear where the mean (19.6%) and standard deviation (8.8%) used to generate the dermal absorption value of 28% come from. As shown in the study report, the mean total percent potentially absorbable for the low dose at 168 hours was determined to be 20.578%, with a standard deviation of 3.152. The derivation of the dermal absorption value of 28% calculated by PMRA would be greatly appreciated.

**PMRA Response:**

The mean potentially absorbable residues included those recovered in all tape strips, as absorption was not complete by the end of the study. Absorption of 75% of the directly absorbed dose had not occurred by the mid-point of the study indicating that the material remaining at the application site may become bioavailable. Hence, tape strips should not be excluded from the potentially absorbed residues.

**15. The following comment was received regarding the occupational exposure of seasonal migrant workers.**

The comment was made that a large portion of the workers in contact with this chemical will be seasonal migrant workers. The commenter said that often the employers will be under only voluntary monitoring of working conditions and so realistically there will be almost nothing in place to protect those who will be coming in the most regular and direct contact with this pesticide.

**PMRA Response**

Pesticides are regulated by Health Canada to ensure they pose minimal risk to human health and the environment. The PMRA registers pesticides after a stringent, science-based evaluation determines they can be used safely when label directions are followed. It also re-evaluates pesticides to confirm products meet current scientific standards. As part of this work, Health Canada carefully considers the safety of farmers, agricultural workers and others who may be exposed to pesticides.

Health Canada is also involved in outreach and education activities, which includes the development of material, such as posters, to inform agricultural workers about the importance of pesticide safety. The target audience for these activities includes seasonal agricultural workers.

The PMRA also has Compliance Officers working across Canada to ensure compliance with the *Pest Control Products Act* and its Regulations. The PMRA responds to incidents, complaints and situations of non-compliance. In addition to the work completed by the PMRA to ensure the safety of agricultural workers, individual provinces also have their own regulators for worker safety. For additional information, refer to <http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/compli-conform/index-eng.php>

**16. The following comment was received regarding the requirement for a respirator and goggles during the handling of the 480 FS formulation or handling of treated seeds.**

It is indicated on pages 4, 7 and 50 of PRD2014-20, that the current draft label would require the use of a NIOSH approved dust mask and goggles during handling of the product and the use of a NIOSH approved respirator by treaters and baggers.

It was commented that the language makes it difficult to discern if there is an intended difference between the general suitable dust mask required during handling the product and treated seed and the NIOSH approved respirator for treaters and baggers in a commercial facility, especially since the label restricts use to commercial treaters. The label language also appears to not address cleanout when the worker is not handling the 480 FS formulation and not handling treated seed. The label language does not clearly address requirements during cleanout of treatment equipment as cleaners are not treaters or baggers.

Also, based on the MOEs in Appendix I, Table 6, of the PRD2014-20, on the inhalation risk assessment and the acute eye irritation classifications, it was proposed that the label not require either goggles or respiratory protection for treaters, baggers, or cleanout personnel, although it had initially been proposed on the draft label submitted.

## PMRA Response

With the exception of the addition of coveralls, the wording of the personal protective equipment statement in question was taken directly from the proposed label submitted by Bayer on 1 October 2012.

"When handling BYI 02960 480 FS or seed treated with BYI 02960 480 FS, work in a well-ventilated area and wear a long-sleeved shirt, long pants, chemical-resistant gloves, and shoes plus socks. DO NOT use leather or cloth gloves. Wear goggles and a suitable dust mask approved by NIOSH/MSHA when handling this product. In commercial facilities, treaters and baggers must wear a NIOSH/MSHA/BHSE-approved respirator."

The workers in the commercial facilities or mobile treaters only have access to the label in which the personal protective equipment requirements include a suitable NIOSH approved dust mask. There would be no confusion with what is printed in PRD2014-20. Cleaners were not included in the original label statement provided by Bayer but will be added in the finalized label statements.

Bayer did not request on-farm seed treatment as such the product is restricted for use in commercial treatment facilities and by mobile treaters.

It is not standard practice for the PMRA to remove personal protective equipment that has been recommended on a proposed label by the applicant. As such, even though the risk assessment did not warrant the requirement for a dust mask or respirator, the dust mask was maintained on the label. The same is true for goggles in that they were not required based on the acute toxicity profile. However, the label has been amended to reflect the proposed change to the personal protective equipment in the comment.

**17. The following comment was received regarding the requirement to wear coveralls during the formulation and handling of treated seeds.**

The comment was in regards to the requirement that coveralls must be worn over a long sleeved shirt and long pants when handling the 480 FS formulation or handling treated seed. The unit dermal exposure data from the Krofski study that was evaluated by PMRA involved the treatment of canola in Canada where coveralls over a long sleeved shirt and long pants was required by the surrogate clothianidin label. In Canada the whole-body dosimeters were placed directly under the workers' coveralls and the whole-body dosimeters were considered the long pants and long-sleeved shirt to comply with the Canadian label. The anticipated variability in clothing worn was anticipated and addressed on page 17 of the study protocol (page 222 of the final study report). Specifically, the protocol stated the following:

"Workers monitored during clothianidin seed treatment in Canada will wear their own outer coverall, plus shoes and socks, over the inner whole-body dosimeters provided by the research team. This will permit compliance with the Canadian label requirements while providing dermal exposure estimates representative of one layer of clothing. It is anticipated that workers may wear additional clothing such as jackets or sweatshirts because of environmental conditions at the time of seed treatment."

Because the study is observational and clothing in addition to a single layer of clothing is expected to be worn, the exposure data are expected to be representative of a label requirement of a single layer of clothing in cold weather conditions. Therefore, the dermal exposure data in the Krotski study are representative of the exposure anticipated for labels requiring long pants and a long-sleeved shirt."

The MOEs for the treaters, baggers, and cleanout personnel were over an order of magnitude greater than the target MOE of 100. PMRA has traditionally used a 50% protection factor for the use of an additional layer of clothing so even adjusting for the potential reduction in exposure to monitored workers who wore jackets or sweatshirts to stay warm, the adjusted MOEs would still exceed 100. The study was designed to estimate exposure based on a single layer of clothing and the results support the use of a single layer of clothing under actual use conditions. Therefore, the commenter requested that the coverall requirement be removed and that treaters and baggers be required to wear long pants and long sleeved shirts:

"Workers involved with treating the seed (for example, connecting and disconnecting hoses and transfer pumps, mixing, equipment calibration, etc.) and others exposed to the concentrate, and cleaners/repairers of seed treatment equipment must wear a long-sleeve shirt and long pants, shoes plus socks, and chemical-resistant gloves. Baggers and others involved in packaging treated seed must wear a long-sleeve shirt and long pants, and shoes plus socks."

#### **PMRA Response**

A review of treater/applicator, bagger/sewer/stacker and cleanout monitoring units (MUs) from the Canadian facilities of the Krotski study did not clearly indicate that a single layer of clothing was worn over top of the whole body dosimeter (WBD). In fact, when a description of the location of the dosimeter was provided in the study, it appeared to be under two layers of clothing in addition to the clothing worn for cold weather climates. Also, the Agricultural Handler Exposure Task Force (AHETF) assessment of the Canadian MUs concluded that all had the dosimeters placed under cotton coveralls and a long-sleeved shirt and long pants. As such, insufficient evidence is available to conclude the unit exposure numbers are reflective of a single layer of clothing.

However, when the treater/applicator MUs in the American facilities were reassessed, dermal and inhalation unit exposure values for closed pour were recalculated without the 5 open pour replicates. Using the revised single layer unit exposure values yielded acceptable MOEs, thus coveralls are no longer required for treaters/applicators (see Table 6 below for the results of the revised risk assessment).

Unit exposure values for the personnel cleaning the canola seed-treatment equipment were considered more appropriate as surrogate data for soybeans as they worked for 8 hours rather than 2 hours for the corn seed-treatment cleanout personnel. Further to this, the cleanout personnel working in facilities treating canola wore two layers of clothing over the dosimeters. As such, cleanout personnel will be required to wear two layers of clothing.

The baggers/sewers/stackers unit exposure values were derived from the MUs which wore gloves. As such, gloves will be maintained on the label.

**Table 6 Exposure & risk estimates for workers in commercial seed treatment facilities treating soybeans with BVT 02940 490 FS**

| Scenario                                        | kg a.i. handled per day | Unit Exposure (µg/kg a.i. handled) |                              | Exposure <sup>1,2</sup> (mg/kg bw/day) |                       | Combined MOE <sup>3</sup> |
|-------------------------------------------------|-------------------------|------------------------------------|------------------------------|----------------------------------------|-----------------------|---------------------------|
|                                                 |                         | Dermal                             | Inhalation                   | Dermal                                 | Inhalation            |                           |
| Treater / Applicator (Single Layer and gloves)  | 28.3                    | 256                                | 2.73                         | $2.54 \times 10^{-5}$                  | $9.67 \times 10^{-5}$ | 296                       |
| Baggers/Sewer/Stacker (Single Layer and gloves) | 28.3                    | 84.7                               | 8.9                          | $2.7 \times 10^{-5}$                   | $3.15 \times 10^{-5}$ | 1380                      |
| Cleanout Personnel (Coveralls and gloves)       | 45 g a.i./100 kg seed   | 56.2 µg/g a.i./100 kg seed/day     | 20 µg/g a.i./100 kg seed/day | $2.85 \times 10^{-5}$                  | $1.13 \times 10^{-5}$ | 553                       |

<sup>1</sup> For treater/applicator and baggers/sewer/stackers

$$\text{Exposure (mg/kg bw/day)} = \frac{\text{Unit exposure (µg/kg a.i. handled per day)} \times \text{kg a.i. handled per day} \times 10^6 \text{ (280% or 35%)}}{80 \text{ kg bw} \times 1000 \text{ µg/mg}}$$

<sup>2</sup> For Cleanout personnel, unit exposures are normalized for application rate (the highest application rate proposed was used) baseline

$$\text{Exposure (mg/kg bw/day)} = \frac{\text{Unit exposure (µg/g a.i./100 kg seed/day)} \times \text{application rate (g a.i./100 kg seed)}}{80 \text{ kg bw} \times 1000 \text{ µg/mg}}$$

<sup>3</sup> Combined MOE = NEHAL (7.8 mg/kg bw/day) ÷ [Dermal Exposure (mg/kg bw/day) + Inhalation Exposure (mg/kg bw/day)], target MOE = 100

In summary, the label personal protective equipment will be revised as follows:

"Treaters/applicators must wear long-sleeved shirt, long pants, chemical resistant gloves and shoes plus socks. Baggers and others involved in packaging the treated seed must wear long-sleeved shirt, long pants, gloves and shoes plus socks. Cleanout/repair personnel must wear coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, and shoes plus socks."

#### 18. A comment was received on environmental residue trials.

The commenter mentioned that PRD2014-20 provides no data on residues, which are a key component to understanding the long-term ecological impacts of flupyradifurone. Although PRD2014-20 claims that "Residue trials conducted throughout Canada, the United States, and Brazil (coffee) using flupyradifurone on a range of representative commodities were deemed acceptable", it was unclear as to who carried out these trials, what the results of these trials were and what their implications are for the environment.

#### PMRA Response:

The residue trials referred to above are crop field trial studies that are intended to elucidate the magnitude of the residues remaining in/on raw agricultural food commodities (RACs) when a pesticide is used according to label directions. As mentioned in PRD2014-20, crop field trial data from field trials conducted in North America with a variety of crops and different application

types (foliar, soil drench, seed treatment) were reviewed by the PMRA. In addition, blueberry trials (lowbush, and highbush) conducted in North America, South America, Australia, New Zealand, and Europe using the same use pattern were also reviewed by the Agency. The number and geographic distribution of trials were determined to be generally in accordance with established international guidelines. Additional information was also submitted to the Agency which demonstrated that residues of flupyradifurone in RACs generally decreased with increasing pre-harvest interval.

The Agency also received separate studies that were designed to determine the fate and behaviour in the environment. This information is included in Section 4.0 of PMR2004-20. Briefly, based on physico-chemical properties, flupyradifurone is soluble in water, is not likely to volatilize from moist soil or water surfaces under field conditions, and it has low potential for long-range transport in the atmosphere. Flupyradifurone is not expected to bioaccumulate in organisms. Laboratory studies showed that depending on the type of soils and climate conditions, rates of flupyradifurone transformation in soils vary considerably (half-lives ranging between 18 to 400 days). Results from field studies showed that dissipation of flupyradifurone exhibited a biphasic behaviour, in other words, a period of rapid loss of approximately 78% of the residue followed by a slow decline of the remaining residue. Overall, 10 out of 12 field dissipation studies resulted in field dissipation half-lives of less than three months. Therefore, although it is characterized as being moderately persistent to persistent, the levels of residue in the environment are expected to remain low.

#### 19. A comment was received about residues in honey.

The commenter asked if it could be guaranteed that eating honey from bees that have come in contact with this chemical would not have an impact on human health.

#### PMRA Response:

As part of the assessment process and prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residue, which are expected to remain on food products, will not be a concern to human health. This maximum amount of residue expected is then legally established as a maximum residue limit (MRL) and is regulated under the *Pest Control Products Act*.

Health Canada sets science-based MRLs to ensure the food Canadians eat is safe. The MRLs set for each pesticide-crop combination are set at levels well below the amount that could pose a health concern. If it is determined that an unacceptable risk exists, the product will not be permitted for sale or use in Canada.

When a specific MRL is not established for a pesticide/crop combination under the *Pest Control Products Act*, the Food and Drug Regulations provide for a general maximum residue limit (GMRL) of 0.1 ppm for residues of agricultural chemicals, and pesticides, on domestically grown and imported food.

As no MRLs have been specified for flupyradifurone in/on honey under the *Post Control Products Act*, residues of this insecticide in honey and honey-derived products must not exceed the CMRL of 0.1 ppm. Nevertheless, it is not anticipated that the consumption of honey containing residues of, or below 0.1 ppm of flupyradifurone, will result in a human health concern, to any subpopulation.

26. Comments were received questioning that the value of flupyradifurone to Canadian agricultural growers has not been demonstrated.

**PMRA Response:**

All proposed uses for a post control product are assessed for value. Value of a post control product is defined under the *Post Control Product Act* as the product's actual or potential contribution to pest management, including product efficacy, effect on host organisms, and health, safety, and environmental benefits and social and economic impact. As part of the registration data requirements, companies must submit a comprehensive value data package to justify product value. This includes information on product performance for controlling proposed pests (for example, control of pests and crop yield) and on sustainability, compatibility with current management practices, resistance management, and benefits, amongst other considerations.

The assessment of flupyradifurone indicated that the uses have value based on several considerations. Flupyradifurone is expected to control labelled pests when they are present at economically damaging levels. Several labelled pests are serious pests of various crops (for example, bean leaf beetle, Colorado potato beetle, blueberry maggot).

Another value consideration is that flupyradifurone can help users with resistance management because it is a new mode of action (NMOA) chemical subgroup (Subgroup ID, 16) (benzimidazole). While compounds in the broader NMOA Group 8 are believed to have the same target site, current evidence indicates that the risk of metabolic cross-resistance between chemical subgroups is low. Many pests on the flupyradifurone label have developed resistance to other chemistries and flupyradifurone provides a new NMOA subgroup for use against these pests. As well, flupyradifurone represents a new NMOA group for use against aphids and leafhoppers on alfalfa.

An additional value consideration is that flupyradifurone has been identified as a potential replacement product for registered uses of diazinon and endosulfan, active ingredients which are being phased out for many pest/crop combinations due to health or environmental concerns. This will provide growers with access to a lower risk product to manage many of the same pests.

27. Comments were received questioning the economic benefit of flupyradifurone, citing international reports which questioned the economic benefit of semiochemical pesticides.

**PMRA Response:**

As with the use of all pesticides, the expected economic return for end users from the use of flupyradifurone is correlated to the prevalence of insect pest populations at levels that exceed economic threshold. Flupyradifurone is expected to provide an economic benefit to end users

when pests are present at economically damaging levels. International reports related to the economic benefits of neonicotinoids appear to have focussed on benefits at the overall soybean industry level rather than those at the farm level. An analysis of the economic benefit of the use of a pesticide at an industry level does not necessarily reflect the potential economic impact of the use of that pesticide at the farm level, which is determined by many factors such as pest pressure, crop, variety/hybrid, soil type, and crop rotation.

22. Some comments expressed concern that the proposed flupyradifurone labels do not address Integrated Pest Management (IPM). In particular, there was a concern that the labels do not encourage alternative pest control practices, and that the labels do not inform the end-user that the presence of target pests should be established before use of a pesticide.

**PMRA Response:**

As outlined in the *Pest Control Products Act* and *Pest Control Products Regulations*, Health Canada's Pest Management Regulatory Agency (PMRA) supports sustainable pest management through the encouragement of good product stewardship, including IPM, and resistance management practices for pest control products. For example, the PMRA supports IPM by working with stakeholders, by the use of resistance management statements on labels, and by encouraging IPM practices. All agricultural labels must have resistance management recommendations which include a statement recommending insecticide use based on an IPM program that includes scouting, record keeping, and considers cultural, biological and other chemical control practices.

23. Comments were received expressing concern about the toxicity of flupyradifurone to bees and the impact the registration may have on bee health. In particular, concern was raised that chronic/sub-lethal exposure of bees to flupyradifurone may not have been properly assessed and more studies are required.

**PMRA Response**

The Department is aware of the importance of bees and the beekeeping industry to the production of food in Canada, as well as the issues regarding bee health, including concerns about potential chronic effects of pesticides. Health Canada scientists are working with scientists from universities and other organizations (for example, Agriculture and Agri-Food Canada, provincial ministries of Agriculture and Environment, the Canadian Association of Professional Apiculturists and other regulatory agencies in the United States and Europe) to determine whether pesticides are contributing to pollinator declines.

Based on study results and using the new tiered risk assessment approach for bees, Health Canada concluded that when used according to label instructions, flupyradifurone is not expected to pose an unacceptable risk to the environment, including pollinators.

In collaboration with international regulatory partners, the PMRA developed and implemented a North American Pollinator Risk Assessment Framework (Pollinator Risk Assessment Guidance, 2014, and USEPA Scientific Advisory Panel, September 2012, which can both be found at <http://www2.epa.gov/pollinator-protection/pollinator-risk-assessment-guidance>). The new

framework employs a tiered approach and considers both adult bees, bee brood as well as multiple exposure routes. Initially, laboratory data (Tier 1) is used along with conservative assumptions. If risks are identified at Tier 1, semi-field (Tier 2) and field studies (Tier 3) are used to further characterize the risk. This new framework strengthens Health Canada risk assessment for bees and improves pollinator protection.

As flupyradifurone is an insecticide and intended to kill insect pests, a certain level of toxicity to bees is expected. In anticipation of this, the applicant submitted a total of 38 toxicity studies that were conducted in accordance with current international test guidelines as well as protocols available in the literature. These studies included laboratory, semi-field and field toxicity studies as well as pollen and nectar residue studies. The majority of studies were semi-field and field studies, each containing a large amount of information. Health Canada, in collaboration with the USEPA and the Australian Pesticides and Veterinary Medicines Authority conducted a thorough review and agreed that these studies met current standards and provided a complete bee toxicity profile of flupyradifurone. The data submitted by the applicant met the requirements set out in the new pollinator risk assessment framework. Study information is summarized at a high level in the text of the PRD2014-20, with a summary of the data found in Appendix I, Table 23, of the document.

Submitted studies not only looked at the toxic effect from acute exposure, they also considered effects from chronic and sub-lethal exposure. For flupyradifurone, six semi-field (confined tunnel) studies and two field studies were evaluated. In the semi-field studies, bees were exposed in confined tunnels to flowers in full bloom that had been sprayed with flupyradifurone for 7-14 days. Mortality, foraging activity, behaviour, colony strength, brood and food development and overall hive vitality were assessed. In the field studies, conservative use scenarios were employed where flupyradifurone was applied at levels much higher than what is being proposed for registration in Canada. This results in bees being exposed to much higher concentrations in the field studies than what is expected with the proposed registration of the product. In these conservative field test scenarios, fields were prepared with one application of flupyradifurone on bare soil immediately before flupyradifurone-treated winter oil-seed was sown, followed in the growing season by two foliar sprays, one at immediate pre-flowering to early flowering and the other at the beginning of full bloom. Bee hives were placed in the field shortly before the pre-bloom spray until the end of flowering period. Bees were actively foraging on the field while both foliar applications were made. The assessments included bee mortality, flight intensity and behaviour of the bees throughout the flowering period. Assessments also included bee health, colony development (including colony strength, colony health, brood- and food development, weight development of the colonies) as well as overall colony vitality throughout the entire monitoring period until the end of overwintering in the following spring. Residues of flupyradifurone in pollen, nectar and wax were analyzed over time until the beginning of overwintering.

Results showed that, in comparison to neonicotinoids, flupyradifurone is much less toxic to individual bees on an acute basis in the laboratory. In addition, study data indicates that flupyradifurone does not cause long-term effects on overwintering adult bees, larvae and bee colonies when tested under semi-field and field conditions.

As a precautionary measure, use restrictions were included on the label to reduce drift and to minimize exposure to pollinators.

- 24. Commenters referred to flupyradifurone as either a neonicotinoid or a neonicotinoid-like chemical, expressing concerns that it will have similar toxic effects in the environment as neonicotinoids, in particular, to bees.**

#### **PMRA Response**

Although flupyradifurone and neonicotinoids all act as nicotinic acetylcholine receptor agonists, the differences in their modes of action resulted in the Insecticide Resistance Action Committee (IRAC) classifying flupyradifurone in a unique sub-group: butenolide (4D, IRAC, 2014), different from the sub-group of neonicotinoids (4B). Data reviewed for flupyradifurone show that it presents a less toxic ecological profile as compared to neonicotinoids, with toxicity to bees under laboratory conditions being much lower than the toxicity of neonicotinoid insecticides.

- 25. A commenter requested more details on the bee studies, such as information on the duration of studies.**

#### **PMRA Response**

The duration of studies is dependent on the test objectives. All laboratory studies submitted by the registrant were conducted in accordance with OECD and USEPA Office of Chemical Safety and Pollution Prevention guidelines, all of which have required study durations. These guidelines can be found at:

- OECD Guidelines for the Testing of Chemicals, ([http://www.oecd.org/env/ehs/testing/oecdguidelinesforthetestingofchemicals.htm#Test\\_Guidelines](http://www.oecd.org/env/ehs/testing/oecdguidelinesforthetestingofchemicals.htm#Test_Guidelines));
- USEPA Final Test Guidelines for Pesticides and Toxic Substances (<http://www2.epa.gov/test-guidelines-pesticides-and-toxic-substances/final-test-guidelines-pesticides-and-toxic>); and
- USEPA Series 850 – Ecological Effects Test Guidelines (<http://www2.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-850-ecological-effects-test-guidelines>).

Field and semi-field studies were conducted following scientifically sound protocols. In the semi-field (confined tunnel) studies, honeybee colonies were exposed to full bloom flowers that were sprayed with flupyradifurone for 4-12 days with additional post-exposure assessments. In field studies, flupyradifurone exposure to honeybee colonies occurred throughout the entire flowering season and the post-exposure assessments included overwintering. Results of 38 bee related studies were presented in the proposed registration decision (PRD2014-20). Table 23 of the PRD2014-20 provided a summary of semi-field (Tier II) and field (Tier III) studies that were evaluated and used in the pollinator risk assessment.

- 26. A question was raised as to whether or not this was an emergency registration.**

#### **PMRA Response**

Flupyradifurone is proposed for full registration. The proposal is not for an emergency registration.

27. A comment pointed out that Table 21 of the PRD2014-20 showed "no data available" for the acute risk quotient for brood for all application types; meanwhile, the chronic risk quotient for brood exceeded levels of concern for foliar application. The commenter also asked if the adult chronic contact risk quotient for foliar application exceeded the level of concern or was indeed "no data available".

#### PMRA Response

The results presented in Table 21 of the PRD2014-20 are for the screening level risk assessment using the most conservative assumptions. Since several RQ values exceeded the level of concern, a higher tiered risk assessment was conducted using semi-field and field studies. The higher tiered assessment indicates that when used according to label direction flupyradifurone is not expected to pose an unacceptable risk to bees.

In addition, Table 21, as presented in the PRD2014-20, is inaccurate and has been updated accordingly.

For flupyradifurone, the risk assessment for bees was conducted in accordance with the recently published North American Pollinator Risk Assessment Framework (Pollinator Risk Assessment Guidance, 2014 and USEPA Scientific Advisory Panel, September 2012). This framework employs a tiered approach. The tier I assessment uses the most conservative assumptions and is based on data obtained from studies conducted under controlled laboratory conditions. The tier I studies include acute adult contact, acute adult oral, chronic adult oral and larvae oral tests and are aimed to investigate effects on individual organisms. Health Canada does not require adult chronic contact studies, as it is unlikely that bees would be exposed to a pesticide for a long period of time through contact. Typically only chronic larvae studies are required by Health Canada as the acute effects can be observed during the initial phase of the chronic study.

To clearly reflect the data requirement for tier I, Table 21 is revised as follows.

**Table 21 Screening Level Estimated Environmental Concentraions and RQ values for honeybees based on foliar, drench, and seed treatment applications.**

| Application Rate    | Life-Stage | Exposure Route |         | Exposure Estimate | RQ                | LOC exceeded? |
|---------------------|------------|----------------|---------|-------------------|-------------------|---------------|
| Foliar Applications |            |                |         |                   |                   |               |
| 200 g a.i./ha       | Adults     | Contact        | Acute   | 0.48 µg a.i./bee  | 0.03 <sup>2</sup> | No            |
|                     |            | Diet           | Acute   | 5.8 µg a.i./bee   | 4.8 <sup>3</sup>  | Yes           |
|                     |            |                | Chronic |                   | 12.5 <sup>4</sup> | Yes           |
|                     | Brood      | Diet           |         | 2.4 µg a.i./bee   | 4.4 <sup>5</sup>  | Yes           |
| Soil Drench         |            |                |         |                   |                   |               |
| 400 g a.i./ha       | Adults     | Diet           | Acute   | 0.026 µg a.i./bee | 0.02 <sup>3</sup> | No            |
|                     |            |                | Chronic |                   | 0.06 <sup>4</sup> | No            |
|                     | Brood      | Diet           |         | 0.01 µg a.i./bee  | 0.02 <sup>5</sup> | No            |
| Seed Treatments     |            |                |         |                   |                   |               |
| 37.75 g a.i./ha     | Adults     | Diet           | Acute   | 0.29 µg a.i./bee  | 0.24 <sup>3</sup> | No            |
|                     |            |                | Chronic |                   | 0.6 <sup>4</sup>  | No            |
|                     | Brood      | Diet           |         | 0.124µg a.i./bee  | 0.2 <sup>5</sup>  | No            |

<sup>1</sup> Based on food consumption rates for larvae (0.124 g/day) and adult (0.292 g/day) worker bees and concentrations in pollen and nectar

<sup>2</sup> LD<sub>50</sub> = 15.7 µg a.i./bee based on acute contact toxicity data for SL 200 G formulation

<sup>3</sup> LD<sub>50</sub> = 1.2 µg a.i./bee based on acute oral toxicity data for TGAI

<sup>4</sup> 10-d NOEC = 0.464 µg a.i./bee/day for adult worker bees

<sup>5</sup> 21-d NOEC = 0.55 µg a.i./larvae/day for bee larvae

- 28. Several comments raised concern about the fact that studies submitted to Health Canada/PMRA are done or paid for by product manufacturers who have a vested interest in economic profit. Another related comment received suggests an independent scientific evaluation be conducted by scientists and governments in other jurisdictions.**

#### PMRA Response

Although studies submitted to Health Canada are sponsored by the product manufacturers, these studies are usually conducted by contracted laboratories and are performed in accordance with international test guidelines (for example, OECD, USEPA Office of Chemical Safety and Pollution Prevention) or other acceptable study protocols. This is standard practice in regulatory Agencies around the world. The protocols used in submitted studies are independently evaluated by Health Canada scientists (and by collaborating global partners as in the case of flupyradifurone).

- 29. Comments received pointed out that Health Canada's risk assessment did not consider synergistic effects on bees as our environment contains a mixture of many pesticides and chemical contaminants.**

#### **PMRA Response**

Additive or synergistic effects of pesticides may be considered in assessments when pesticides have common modes of action and are known to co-occur in the environment, for instance, when used in combination through tank mixing or co-formulations in the same end-use product. When information on synergistic or additive effects is available, it is taken into consideration in the risk assessment. As an example, a submitted bee study was conducted with a mixture of flupyradifurone and tebuconazole (an azole fungicide). This study showed that there were synergistic effects between flupyradifurone and tebuconazole and as a result the label restricts the use of flupyradifurone with azole fungicides as a tank mix.

- 30. A comment was received suggesting the use of flupyradifurone be restricted to use within the framework of an established IPM system, ensuring that the target pest(s) is (are) present before applying flupyradifurone. Another comment was received suggesting that farmers should not rely only on pesticides and should also use alternative farming practices such as diversifying crop rotations, altering the timing of planting, tillage and irrigation, using less sensitive crops in infested areas, applying biological control agents and other lower-risk alternatives.**

#### **PMRA Response**

Health Canada supports sustainable pest management through the encouragement of good product stewardship, including IPM, and resistance management practices for pest control products. For example, the PMRA supports IPM by working with stakeholders, by the use of resistance management statements on labels, and by encouraging IPM practices. All agricultural labels must have resistance management recommendations which include a statement recommending insecticide use based on an IPM program that includes scouting, record keeping, and considers cultural (for example, planting practices), biological and other chemical control practices. Practices such as crop rotation are employed in the IPM programs to help control pest populations. Pesticides are used in conjunction with these practices to ensure healthy crops.

- 31. Questions were received regarding the effectiveness of mitigating risk to bees by restricting applications to the early morning and evening during bloom. One commenter indicated that "no foliar spray applications to honeybee-pollinated crops that are currently in flower should be allowed". One commenter also asked why measures to reduce the exposure to bees are less stringent than the neonicotinoids.**

#### **PMRA Response**

As explained in the response to Comment 24, flupyradifurone is classified in a unique sub-group of nicotinic acetylcholine receptor agonists: butenolide (4D, IRAC, 2014), different from the sub-group of neonicotinoids (4B). Data reviewed for flupyradifurone show that it presents a less toxic ecological profile as compared to neonicotinoids, with much lower toxicity to bees.

In assessing risk to bees, Health Canada carefully evaluated a number of tier 2 and tier 3 bee toxicity studies submitted by the applicant, in addition to laboratory studies. Tier 2 studies consisted of semi-field studies where flupyradifurone was fed directly to colonies, or studies where bees were allowed to forage on residues following multiple applications of the compound at the maximum label rate, including foliar applications at full bloom while bees were actively foraging. Tier 2 studies also included measurements of residues in plant matrices such as pollen and nectar. Tier 3 studies were conducted under field conditions where oil-seed rape seeds were treated with BYI 02960 480 FS, sown into soil treated with Sivanto Prime Insecticide, and given two foliar applications of Sivanto Prime Insecticide, including one application at full bloom when bees were actively foraging. It was concluded that although there were some short-term effects observed on mortality and foraging, they did not result in detectable effects on colony development (including colony health, brood development, food storage, and colony weight), overall colony vitality or overwintering success.

The label instructions for foliar application of flupyradifurone indicate that as a precautionary measure to further minimize any short-term effects on adult honeybees and to minimize any effects to native pollinators that may include solitary bees, spraying should be done in the early morning or evening when bees are not expected to be foraging.

When label directions are followed, the use of flupyradifurone is not expected to result in unacceptable risk to pollinators.

- 32. Questions were received regarding the effectiveness of mitigating risks and enforcement of mitigation measures: How does seed tag information mitigate risk to birds and mammals through ingestion of treated seed? How are precautionary label statements regarding leaching, run-off and carry-over enforced. How are buffer zones enforced?**

#### **PMRA Response**

Information provided on the seed tag label informs users about the potential risk to birds and mammals and instruct users to incorporate/bury any spills or exposed seeds into soils.

The precautionary label statements regarding leaching, run-off and carry-over are not meant to be enforced. They are included on the label to inform users that best management practices should be followed to reduce the potential for runoff.

With respect to no-spray buffer zones, mandatory mitigation measures are printed on product labels and users are required to read and follow label instructions. Health Canada routinely inspects pesticide users for compliance with pesticide labels directions. Regional staffs conduct inspections, respond to complaints and follow up on all suspected pesticide misuse. Enforcement action is taken when there is evidence of label violations and these enforcement actions can range from education, to warnings, orders or penalties, depending on the nature and severity of the offence. Pesticide labels contain instructions for the safe use of the pesticide and users are expected to follow all of the label directions.

It is these label instructions, such as buffer zones, that regional staff are verifying for compliance during their inspections. Buffer zones specified on the label are for the protection of environmentally sensitive habitats such as aquatic habitat, forests, grasslands etc. Protection of humans, wildlife and insects, that fall outside of sensitive habitats, are addressed elsewhere on the label.

- 33. Several comments were received raising concern about the persistence of flupyradifurone in the environment, in particular, in the turbid aquatic environment, allowing it to build up gradually in the environment and enter aquatic habitat through runoff. One commenter asked what is the likelihood that flupyradifurone will enter the sensitive habitats. Commenters suggested including the degree of persistence of a pesticide as a criteria in registration approvals, to have measures in place to ensure flupyradifurone does not buildup in the environment and to require monitoring as a condition of registration.**

#### **PMRA Response**

Persistence of a pesticide is considered during the fate characterization and risk assessment processes. For flupyradifurone an array of laboratory fate studies showed that it is very soluble in water, does not strongly adsorb to soil particles and is moderately persistent to persistent under Canadian climatic conditions (slightly persistent in warmer climates). Such properties suggest that flupyradifurone has the potential to move away from the site of application and enter surface water through run-off and groundwater through leaching.

Groundwater (PRZM-GW) and surface water (PRZM/EXAMS) modelling conducted by Health Canada took into account chemical fate data, the proposed product use pattern and historical weather data to estimate 50-year trends of environmental concentrations for five representative sites across Canada. The results indicated that when used according to the label instructions, levels of flupyradifurone in the environment would not pose unacceptable risk to human health or the environment.

Results obtained from twelve terrestrial field dissipation studies in North America and Europe including three sites in Canada did not detect flupyradifurone residues below a soil depth of 30 cm over a period of 1.5 years.

Health Canada has not proposed the requirement for mandatory post-registration environmental monitoring for flupyradifurone as under the approved conditions of use, it is not expected to pose any unacceptable risk to human health or the environment.

34. Concern was raised about the long-term consequences of the use of flupyradifurone, citing DDT and neonicotinoids as examples. Concern was raised that not enough time is available to allow the study of the long term consequences of use before pesticides are registered. Commenters expressed concern about the fixed 15 year re-evaluation cycle, suggesting that it is too long to wait and that in the past, lawsuits have had to be threatened in order to get re-evaluations done sooner.

#### **PMRA Response**

To register a pesticide for use in Canada, a broad range of environmental fate and toxicity data need to be generated. These data allow Health Canada to conduct a thorough assessment of both short-term and longer-term risks to human health and the environment.

DDT was banned in 1972 as it was shown to be extremely persistent (half-life of 2 to 16 years) and it bioaccumulated and biomagnified in the environment. In comparison, flupyradifurone has a half-life of 38 to 400 days and it is not expected to bioaccumulate in the environment. Data reviewed for flupyradifurone indicate that it has a different ecological toxicity profile than the neonicotinoids, including much lower toxicity to bees.

Health Canada applies a science-based approach to regulate pesticides. We will continue to work with national and international colleagues to closely monitor scientific information and other developments related to potential impacts of pest control products, not only in Canada and the United States, but also in Europe. Should the available science indicate unacceptable risk to the environment or human health, additional regulatory measures will be taken.

35. Comments were received raising concern about risks to other non-target organisms.

#### **PMRA Response – Earthworm Toxicity**

Several earthworm toxicity studies were conducted in accordance with internationally acceptable test guidelines or protocols. The submitted studies include acute and chronic laboratory studies using flupyradifurone technical, the formulation product Sivanto Prime Insecticide, as well as two soil transformation products 6-CNA and DFA. In addition, a field study was also conducted with Sivanto Prime Insecticide at a much higher application rate than the label rate. Though some adverse effects such as mortality on acute basis and effects on juvenile growth and survival on chronic basis were observed in the laboratory studies at relatively high doses, the field study showed that there was no unacceptable adverse effects on abundance and biomass of total earthworm population at 1500 g a.i./ha, more than 3 times of the maximum annual application rate on the label. The field observation is consistent with the results of risk assessment based on the maximum allowable soil application rate and the most sensitive toxicity endpoints. The calculated risk quotients (RQ) were < 0.2 for all chemicals tested. Therefore, Health Canada has concluded that there is no unacceptable risk to earthworms.

#### **PMRA Response - Beneficial Arthropod Toxicity**

Consistent with the intended use, flupyradifurone has shown some toxic effects to several indicator species when exposed at high enough concentration. The semi-field studies conducted with parasitoid wasp (*Aphidius rhopalosiphii*) and predatory bug (*Orius laevigatus*) showed that

when the organisms were exposed to residues of Sivanto Prime Insecticide aged on leaves, mortality and reproduction recovered gradually and near 100% recovery was observed after 56 and 42 days, respectively. Toxicity effects of flupyradifurone at the community and population levels were investigated in two field studies where beneficial organisms in grassland habitat were exposed to flupyradifurone by direct foliar application. Results showed that the affected population rebounded over time and there were no statistically significant effects on prevailing arthropod communities at testing rates of 21 g a.i./ha. Based on these results, Health Canada concluded that the affected population is likely to recover within a reasonable time and thus the risk to beneficial insects is acceptable.

#### **PMRA Response – Bird and Mammal Toxicity**

Studies showed that flupyradifurone has adverse effects on some species of birds and small wild mammals when exposed through ingestion. The risk is, however, considered minimal as the risk assessment was performed using the most conservative approach by assuming the highest allowable application rates, the contaminated food items were the only available food sources, as well as applying a 10 fold uncertainty factor as an added measure of protection. For foliar and soil applications the risk assessment showed that the risk quotients (RQ) were only slightly above the level of concern (LOC) when on-field exposure with maximum nomogram residues was considered. The RQ values, however, were below LOC when off-field exposure with mean nomogram residues was considered. Overall, because the likelihood for birds and mammals to only consume contaminated food items is low, and the predicted RQs only slightly exceeded the LOC in some scenarios, the risk to these animals is expected to be minimal.

When flupyradifurone is used for soybean seed treatment, a potential risk was identified for medium sized mammals (with a generic body weight of 35 grams) only. Consequently, measures are required to minimize exposure to treated seed. The measures include the following instructions, which will be placed on seed-tags for treated seeds and product labels:

*Any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned-up from the soil surface. Left over treated seed should be double-sown around the headland, or buried away from water sources.*

#### **PMRA Response - Aquatic Invertebrate Toxicity**

An array of acute and chronic studies, conducted with flupyradifurone and its transformation products including difluoroacetic acid (DFA), 6-chloro-nicotinic acid (6-CNA), BYI 02960-succinamide and BYI 02960-azabicyclo-succinamide, was submitted for review. Results showed that all transformation products are less toxic than the parent compound. Likewise, risk assessment showed that only parent compound poses a potential risk to this group of organisms if they were exposed through run-off and spray drift. In order to mitigate risk to aquatic organisms from spray drift, spray buffer zones are specified on the label. In order to inform users of the risk to aquatic organisms from run-off, a precautionary statement advising users to minimize run-off is included on the label.

### PMRA Response - Bioaccumulation in Fish

The potential for bioaccumulation in fish is assessed based on the physico-chemical properties of flupyradifurone. This chemical is highly soluble in water (3.2 g/L at 20°C) and has a low *n*-octanol-water partition coefficient ( $\log K_{ow}$  1.2 at pH 4, 7 and 9). Based on this information the potential for flupyradifurone to bioaccumulate is considered to be low.

36. Concern was expressed with respect to the proposed buffer zones, saying that they are arbitrary and completely unsupported by data, not taking into account soil type, rainfall and snowmelt, proximity to sensitive areas such as wetlands, and drainage.

### PMRA Response

The purpose of establishing a spray drift buffer zone is to protect sensitive habitats that are downwind of a pesticide application from unacceptable levels of pesticide drift. The PMRA determines the size of buffer zones based on the potential risk identified to off-target sensitive habitats (for example, terrestrial or aquatic habitats, wetlands and riparian zones), taking into account the spray equipment used. Buffer zones are specific to the sprayer type used (for example, field boom sprayer, airblast sprayer or aerial application), application conditions identified on the label (for example, spray droplet size, spray height, wind conditions), and the application rate for the commodity being sprayed (for example, crop type).

37. Concern was raised regarding the lack of information for several transformation products including 6-chloronicotinic acid, difluroacetic acid, BYI 02960-succinamide, BYI 02960-azabicyclooctinamide and 2-chloropyridine, and their effects on the environment.

### PMRA Response - 6-chloronicotinic acid (6-CNA)

6-chloronicotinic acid (6-CNA) was observed as a major transformation product in one of the laboratory soil degradation studies, accounting for a maximum of 11.6% of applied radioactivity (AR). A separate soil transformation study was conducted using radio-labelled 6-CNA as the starting material. Results of this study showed that 6-CNA degrades rapidly to predominantly CO<sub>2</sub> (accounted for 84-92% of AR) and bound residues (9.7-14.5% of AR).

The toxic effects of 6-CNA were tested on earthworm, bees, terrestrial and aquatic invertebrates and green algae. Although many of these tests were conducted with a single dose, the concentrations used were much greater than the anticipated environmental concentrations based on the maximum allowable application rate. No adverse effects were observed in these tests. Therefore, it is concluded that the amount of 6-CNA formed in the environment as a result of flupyradifurone application will not result in unacceptable risk to the environment.

Given that 2-chloropyridine is not formed in the environment from the use of flupyradifurone-containing products, human exposure to this compound is not anticipated to occur and therefore there is no human health risk of concern.

### PMRA Response – difluoroacetic acid (DFA)

Difluoroacetic acid (DFA) was observed as a major transformation product of flupyradifurone in aerobic soils under laboratory conditions, accounting for a maximum of 34% of AR. Subsequent toxicity studies conducted for earthworm, bees, terrestrial and aquatic invertebrates, green algae and fish species showed that DFA had no observable effects on aquatic organisms and was less toxic to earthworms, bees and terrestrial arthropods than the parent compound. Although many of these tests were conducted with a single dose, the concentrations used were orders of magnitude higher than the anticipated environmental concentrations based on the maximum allowable application rate. Therefore, it is concluded that the amount of DFA formed in the environment as a result of flupyradifurone application will not result in unacceptable risk to the environment.

### PMRA Response - BYI 02960-succinimide and BYI 02960-azabicyclonuccinimide.

Flupyradifurone transformation products BYI 02960-succinimide and BYI 02960-azabicyclonuccinimide were only observed in an aqueous phototransformation study in which flupyradifurone was added to either a pH 7 buffer solution or water taken from a lake in Kansas and irradiated under artificial light. These two compounds were not formed in the soil phototransformation study. Thus, limited amounts of these two compounds will be formed in the environment as phototransformation can only occur in shallow clear water bodies or the thin top layer of deeper water bodies where light can penetrate. Furthermore, the review of aquatic insect and fish toxicity studies conducted with BYI 02960-succinimide and BYI 02960-azabicyclonuccinimide showed no adverse effects on organisms. Therefore, there is a reasonable certainty that the formation of BYI 02960-succinimide and BYI 02960-azabicyclonuccinimide through aqueous phototransformation will not cause harm to aquatic organisms.

### PMRA Response - Formation of 2-chloropyridine

A commenter pointed out that 2-chloropyridine is a persistent chemical and has been classified as a probable carcinogen; however, this chemical was not captured in the transformation studies because the pyridine ring was not labelled. The commenter also mentioned that there were previous queries regarding the chemical.

In response, PMRA can confirm that several aerobic soil studies were conducted with the pyridine ring labelled flupyradifurone and 2-chloropyridine was not observed. Furthermore, although a number of group 4 insecticides (including flupyradifurone and imidacloprid) contain 2-chloropyridine in their molecular structures, an internal database search showed that none of these chemicals produced 2-chloropyridine in chemical and biological transformation studies. A search of available literature yielded no additional information regarding 2-chloropyridine being produced as a transformation product of any insecticide. Based on inspections of the chemical structure and the proposed transformation pathways of flupyradifurone, the most probable precursor to form 2-chloropyridine would be decarboxylation of 6-chloronicotinic acid (6-CNA). However, a submitted study conducted with  $^{14}\text{C}$  labelled 6-CNA (labelled at 2 and 6 positions of the pyridine ring) showed that 6-CNA transformed rapidly in aerobic soils, forming  $^{14}\text{CO}_2$  (84–92% AR), non-extractable residues (9.7–14.3% AR) and two unknown components (at maximum of 3 and 5% AR, respectively). These results do not suggest the formation of 2-chloropyridine. The formation of  $^{14}\text{CO}_2$  is indicative of pyridine ring fusion. The transient nature of the two

unknown (non-detectable within 14-31 days) suggests that they are not likely to be 2-chloropyridine, as it is understood to be persistent. Finally, 2-chloropyridine is highly soluble in water (25 g/L at 25°C) and diethyl, and thus, if it were formed, it would be detected in the ammonium acetate/methanol (20:80 v/v) extracts. Therefore, at the present time, Health Canada has no evidence to suggest that 2-chloropyridine is a breakdown product of flupyradifurone.

38. One commenter indicated that the emission of CO<sub>2</sub> through breakdown of flupyradifurone will have an impact on global warming. Based on the assumption that flupyradifurone would be used to replace all the neonicotinoids, it would be about 20% of all insecticides in the world market.

#### **PMRA Response**

The environmental risk assessment of pesticides conducted by the PMRA does not consider the impact of CO<sub>2</sub> generated during the breakdown of pesticides and the subsequent contribution to global warming. The quantities of CO<sub>2</sub> produced through breakdown of flupyradifurone are considered insignificant in comparison to various other sources.

39. Flupyradifurone is on the List of Substances Scheduled for Evaluation and Request for Data for the joint FAO/WHO Meeting on Pesticide Residues 2015 meeting, Geneva, scheduled for September 15-24, 2015. The commenters urge Health Canada to wait and make the decision accordingly.

The period during which FAO/WHO was soliciting toxicological and residue chemistry data of pesticides, including flupyradifurone, for review at the JMPR meeting in September 2015, closed on 31 December 2014. The intent of the meeting is not for environmental or occupational risk assessment. Therefore, the outcome of the FAO/WHO evaluation report will not likely impact on Health Canada's occupational and environmental risk assessment. However, if relevant data were received, Health Canada will consider them.

40. Comments were received inquiring how Health Canada would address First Nations concerns with respect to the environmental fate of flupyradifurone.

#### **PMRA Response**

The environmental fate of flupyradifurone has been addressed during the scientific review of this compound, and is also addressed in several responses to comments received during the consultation.

41. A comment was received urging Health Canada to employ the precautionary principle.

#### **PMRA Response**

More than 150 studies were submitted related to the environmental behaviour and ecotoxicology of flupyradifurone. Sufficient data has been provided to allow Health Canada to conclude that, when used according to label directions, flupyradifurone does not present an unacceptable risk to the environment, including pollinators.

62. A ~~consensus~~ believes that Health Canada only registers products for sale in Canada.

**PHRA Response**

Health Canada's top priority is not only to protect the health and safety of Canadians, but also their environment and their food supply. This is accomplished by applying stringent health and environmental standards when making regulatory decisions. Before a product is approved for use in Canada, it must undergo a thorough science-based assessment. Environmental risk assessments require data on the fate of the pesticide in the environment as well as toxicity studies on various species (birds, bees and other non-target insects, non-target plants, freshwater and marine fish species, algae and other aquatic organisms). Study results are used to estimate environmental concentrations, which are subsequently used for risk assessment. If the use of a product poses unacceptable risks to human health, future generations or the environment, Canadian registration is not granted.

63. ~~Comments were received requesting the delay of the registration of fipronil/fipronate until (1) results of several years of independent third party research on the effects of fipronil/fipronate on bees and other useful insects become available; and (2) bee colonies have had a chance to recover.~~

**PHRA Response**

Health Canada has concluded that, when used according to label directions, fipronil/fipronate does not present an unacceptable risk to the environment, including pollinators. Health Canada applies a science-based approach to regulate pesticides. We will continue to work with national and international colleagues to closely monitor scientific information and other developments related to potential impacts of pest control products on pollinators, not only in Canada and the United States, but also in Europe. Additional regulatory measures will be taken if warranted and supported by the available science.

64. ~~One commentor suggested applying the Sir Bradford Hill's 9 criteria determining a cause and effect relationship to determine a cause and effect relationship between exposure to an agent and associated health effects.~~

**PHRA Response**

The PHRA uses internationally recognized approaches, including the Bradford Hill criteria when appropriate, in evaluating the risks of pesticides to human health and the environment. These approaches are used by regulatory agencies around the world including the United States, Europe, and Australia. The PHRA works with our international partners to update our risk assessment approaches so that they meet modern scientific standards. The new pollinator risk assessment framework is an example of this process.